

### Remarks

Applicants appreciate the thorough examination of the present application as evidenced by the Office Action dated March 24, 2006 (hereinafter, the "Office Action"). Claims 16, 22, 31-33 and 41-43 are pending in the present application, and these claims stand rejected. Applicants have canceled Claim 41 without prejudice. Applicants have amended Claims 16, 31 and 43. Applicants do not believe that any new matter is introduced by these claim amendments, as will be discussed in detail below, and the entry of these amendments is respectfully requested. Applicants further respectfully submit that the present application is in condition for allowance for at least the reasons set forth below.

#### **I. Claim Rejections Under 35 U.S.C. §102(b) in View of Silvestris et al.**

Claims 16 and 31-33 stand rejected under 35 U.S.C. § 102(b) as being anticipated by Silvestris et al. *Ann Hematol.* **70(6)**: 313-318 (1995) (hereinafter, "Silvestris et al.") for reasons previously made of record. *See* Office Action, page 2. In particular, the Office Action dated December 28, 2004 stated that "it is clear that the administration of a chemotherapeutic regimen as taught by Silvestris et al. caused endothelial damage mediated by mechanical damage, inflammation, and heart disease and therefore, the administration of epo to this population would inherently treat endothelial injury as claimed. . . . In the absence of evidence to the contrary, the method of Silvestris et al. would also inherently reduce the suppression of endothelial cells growth and increase the number of endothelial cells growth as claimed." December 2004 Office Action, pages 3-4.

As noted in the Office Action, Applicants have previously asserted that Silvestris et al. does not teach administration of an endothelial-protecting amount of erythropoietin (EPO) as provided by the pending claims. *See* Office Action, page 2. Instead, the patient population presented in Silvestris et al. was multiple myeloma patients undergoing second-induction chemotherapy. Thus, these patients received initial chemotherapy treatment *followed* by EPO administration.

In order to clarify the recitations directed to the distinct methods of the pending claims, Applicants have amended Claims 16, 31 and 32 to recite that "erythropoietin is administered prior to *initial* administration of said chemotherapeutic agent" (emphasis added). Applicants respectfully submit that support for these claim amendments can be found in the specification as originally filed. More specifically, Applicants submit that, upon

a fair reading of the specification, a person of ordinary skill in the art would recognize in the present disclosure that the timing of EPO administration "prior to" administration of a chemotherapeutic agent conveys administration prior to the initiation, *i.e.*, before the first dose, of chemotherapy. As demonstrated in the specification, EPO can protect and/or repair endothelial cells and the endothelium from toxicity induced by chemotherapeutic agents when EPO is administered before administration of the particular agent. Turning specifically to the specification, Figure 4 presents a graph showing the responses of endothelial cell cultures exposed first to varying dosages of EPO and, two hours later, to cisplatin (compared to control endothelial cell culture exposed only to cisplatin). Clearly, the EPO was provided to the cells prior to any previous exposure of the cells to cisplatin. This protocol sets forth the protocol for administering EPO to patients prior to the **initial** administration of a chemotherapeutic agent to treat and/or reduce endothelial injury.

Applicants respectfully assert that, upon application of the appropriate standard for evaluating patent claims for adequate written description, it is apparent that the claims of the present invention meet this requirement. A review of the case law reveals that the courts have consistently held that it is well established that there is no *in haec verba* requirement and that newly added claim limitations can be supported in the specification through **express, implicit, or inherent disclosure**. See "Written Description" Requirement as published on January 5, 2001 in the Federal Register (Vol. 66, pages 1099-1111), page 1105, first column of the Guidelines for Examination of Patent Applications Under the 35 U.S.C. 112, ¶ 1. Moreover, the Court of Customs and Patent Appeals (CCPA) has stated that "[t]he function of the description requirement is to ensure that the inventor had possession, as of the filing date of the application relied on, of the specific subject matter now claimed by him; how the specification accomplishes this is not material . . . . It is not necessary that the application describe the claim limitations exactly . . . but only so clearly that persons of ordinary skill in the art will recognize from the disclosure that applicants invented processes including those limitations." (*In re Wertheim*, 541 F.2d 257 (CCPA 1976), citing *In re Smith*, 482 F.2d 910 (CCPA 1973) and *In re Smythe*, 480 F.2d 1379 (CCPA 1973). Thus, Applicants respectfully submit that the claim amendments are supported in the specification through explicit, implicit or inherent disclosure.

Concerning the declaration of Dr. George Sigounas filed under 37 C.F.R. §1.132, Applicants recognize that such a declaration cannot be used to overcome a rejection under 35

U.S.C. §102(b). Applicants respectfully submit that Silvestris et al. is not an enabling reference, and one skilled in the art would not be in possession of the present invention on the basis of combining one's own knowledge with the disclosure presented in Silvestris et al. The Sigounas Declaration was submitted by Applicants in further support of the proposition that neither Silvestris et al. nor any of the other cited references provide an enabling disclosure under 35 U.S.C. §102(b) where the declaration shows, as noted in the Office Action, "prior to the instant invention, those of skill in the art would not administer EPO before the treatment with chemotherapeutics, instead the skilled artisan would only administer EPO following the diagnosis of anemia." Office Action, page 3.

Thus, at least in view of the claim amendments and the lack of enabling disclosure provided by Silvestris et al., Applicants respectfully submit that Claims 16 and 31-33 are not anticipated by Silvestris et al., and Applicants respectfully request that these claim rejections be withdrawn.

## **II. Claims Rejections Under 35 U.S.C. §102(b) in View of JP 02 096535**

Claims 16, 22, 31-33 and 41-43 stand rejected 35 U.S.C. § 102(b) as being anticipated by JP 02 096535 to Chugai Pharm. Co. Ltd. (hereinafter, "the Chugai reference") for reasons previously made of record. *See* Office Action, page 4. More specifically, the Office Action dated December 28, 2004 stated that "it is clear that the administration of a chemotherapeutic regimen as taught by the JP 02 096535 abstract caused endothelial damage mediated by mechanical damage, inflammation, and heart disease and therefore, the administration of epo to this population would also inherently treat endothelial injury as claimed." December 2004 Office Action, page 5.

As noted above, in order to clarify the recitations directed to the distinct methods of the pending claims, Applicants have amended Claims 16, 31 and 32 to recite that "erythropoietin is administered prior to initial administration of said chemotherapeutic agent." Claim 43 has been amended to recite that EPO is administered "prior to initial administration of said cisplatin." Applicants respectfully submit that the Chugai reference does not teach administration of EPO prior to initial administration of the chemotherapeutic agent. Instead, the patient population presented in the Chugai reference received EPO only after being diagnosed with anemia as a result of previously receiving chemotherapy.

Thus, at least in view of the claim amendments and the lack of enabling disclosure provided by the Chugai reference, Applicants respectfully submit that Claims 16, 22, 31-33, 42 and 43 are not anticipated by the Chugai reference, and Applicants respectfully request that these claim rejections be withdrawn.

### **III. Claims Rejections Under 35 U.S.C. §102(b) in View of Bukowski et al.**

Claims 16 and 31-33 stand rejected under 35 U.S.C. § 102(b) as being anticipated by Bukowski et al. *Blood* **84 (10 Supp. 1):** 129A (1994) (hereinafter, "Bukowski et al.") for reasons previously made of record. *See* Office Action, page 4. The December 28, 2004 Office Action stated that "it is clear that the administration of a chemotherapeutic regimen as taught by Bukowski et al. caused endothelial damage mediated by mechanical damage, inflammation, and heart disease and therefore, the administration of epo to this population would inherently treat endothelial injury as claimed." December 2004 Office Action.

As previously noted, in order to clarify the recitations directed to the distinct methods of the pending claims, Applicants have amended Claims 16, 31 and 32 to recite that "erythropoietin is administered prior to initial administration of said chemotherapeutic agent." Applicants respectfully submit that Bukowski et al. does not teach administration of EPO prior to initial administration of the chemotherapeutic agent. Instead, the patient population presented in Bukowski et al. was anemic cancer patients. Thus, these patients received EPO after being diagnosed with anemia and only after receiving chemotherapy.

Thus, at least in view of the claim amendments and the lack of enabling disclosure provided by Bukowski et al., Applicants respectfully submit that Claims 16 and 31-33 are not anticipated by Bukowski et al., and Applicants respectfully request that these claim rejections be withdrawn.

### **IV. Claims Rejections Under 35 U.S.C. §103 in View of the Cited References**

Claims 16, 22, 31-33 and 41-43 stand rejected under 35 U.S.C. § 103 as being obvious in view of the combination of Silvestris et al. or Bukowski et al. in view of the Chugai reference for reasons previously made of record. *See* Office Action, page 5.

In order to establish a *prima facie* case of obviousness, three basic criteria must be met. First, the cited reference or combination of references must teach or suggest all the claim recitations. *See In re Wilson*, 165 U.S.P.Q. 494 (C.C.P.A. 1970). Second, there must

be some suggestion or motivation, either in the references themselves or in the knowledge generally available to one of ordinary skill in the art, to modify the reference or to combine reference teachings in order to arrive at the claimed invention. *See In re Oetiker*, 24 U.S.P.Q.2d 1443, 1446 (Fed. Cir. 1992); *In re Fine*, 837 F.2d at 1074; *In re Skinner*, 2 U.S.P.Q.2d 1788, 1790 (Bd. Pat. App. & Int. 1986). Third, there must be a reasonable expectation of success. *See* M.P.E.P. § 2143.

For at least the reasons discussed above in Sections I-III, none of the cited references teach the recitations of the pending claims. Additionally, Applicants respectfully submit that there is no suggestion or motivation, either in the references themselves or in the knowledge generally available to one of ordinary skill in the art, to modify the references or to combine the reference teachings. As shown in the previously submitted Sigounas Declaration, it was not routine practice to administer EPO prior to diagnosing a patient with anemia caused by, among other things, chemotherapeutic agents. Instead, patients received EPO to treat anemia after initiation of chemotherapy. Thus, it was not routine practice to administer EPO prior to the initial administration of chemotherapy. Accordingly, there is no proper motivation to modify the cited references to achieve the methods recited in the pending claims. Additionally, Applicants submit that there clearly would not have been a reasonable expectation of success of arriving at the present invention where the pending claims are directed to methods that were not routine practice at the time of filing the application and are not described in the cited references.

Lastly, the Office Action states that "the claims of the instant invention encompass a range beyond what is provided in the declaration." Office Action, pages 5-6. Applicants note that the dosage used in the studies referenced in the Office Action was 60 Units per mouse. 60 Units per mouse corresponds to approximately 2000 Units per kilogram. Thus, Applicants respectfully submit that the data provided in the Sigounas Declaration are commensurate in scope with the pending claims.

Accordingly, Applicants respectfully submit that Claims 16, 22, 31-33, 42 and 43 are not obvious in view of any combination of the cited references, and Applicants respectfully request that these claim rejections be withdrawn.

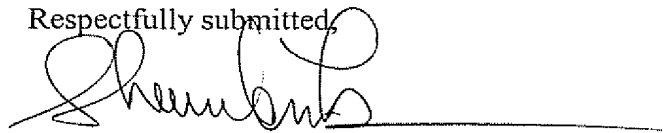
**V. Summary**

None of the cited references teach or suggest administering EPO prior to initial administration of a chemotherapeutic agent. As recited in the amended claims, EPO is administered prior to initial administration of a chemotherapeutic agent. The cited references do not teach the methods recited in the pending claims. Moreover, at least in view of the remarks presented above, one of ordinary skill in the art would not be motivated to administer EPO prior to initial administration of a chemotherapeutic agent absent the teachings of the present invention.

**Conclusion**

In view of the foregoing amendments and remarks, Applicants respectfully request that all outstanding rejections to the claims be withdrawn and that a Notice of Allowance be issued in due course. The Examiner is invited and encouraged to contact the undersigned directly if such contact will expedite the prosecution of the pending claims to issue. In any event, any questions that the Examiner may have should be directed to the undersigned, who may be reached at (919) 854-1400.

Respectfully submitted,



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